AL03 **Physiological and Pathophysiological Functions of Ion Channels as a Target of Drug Therapy and Discovery**

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Ion channels are membrane proteins, which are essential to promote significant cellular functions, such as action potential generation, its conduction, transmitter release, contraction, and hormone release, in excitable cells, including neurons, muscles and secretory cells. Thus, ion channel malfunction directly results in a disease and/or pathophysiological setting. Even in non-excitable cells, ion channel activities contribute to proceed several cellular stages of cell proliferation, differentiation and occasionally also cell death.

Smooth muscle (SM) is one of major components in visceral organs and contributes to produce tissue tone and/or organ movement. SM disorders are always potential targets of drug therapy. A contraction in SM is induced by the rise of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) as well as in skeletal and cardiac muscles. The Ca^{2+} mobilization patterns in SMs are multiple depending upon organs and their excitability. The patterns can be clearly described based on the types and densities of ion channels, such as voltage-dependent Ca^{2+} channels (VDCC). we succeeded to record simultaneously Ca^{2+} images of spontaneous Ca^{2+} release (Ca^{2+} spark) from local sarcoplasmic reticulum (SR) through ryanodine receptors (RyRs) and spontaneous transient outward currents (STOCs) due to the activation of large conductance Ca^{2+} activated K^+ channels (BK_{Ca}) by Ca^{2+} sparks. This revealed a negative feedback mechanism underlying the control of $[Ca^{2+}]_i$ via BK_{Ca} activation in SM. Single molecule visualization techniques allowed us to determine molecular assembly responsible for translating Ca^{2+} signals to electrical ones in Ca^{2+} microdomain and caveolae (Fig.1).

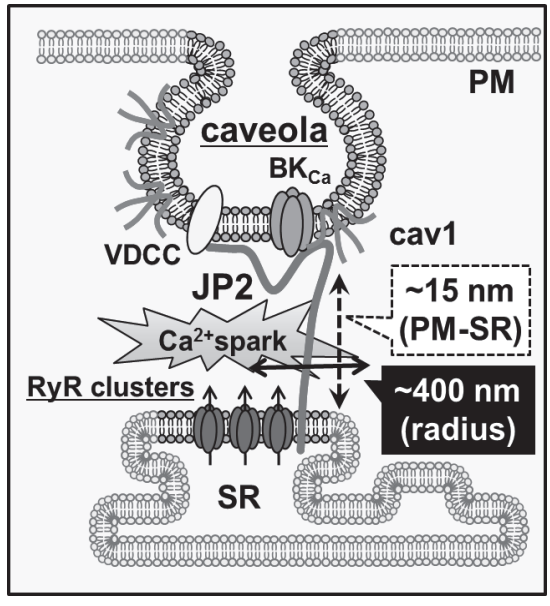

Fig.1 Complex of functional molecules accumulated in a Ca^{2+} microdomain

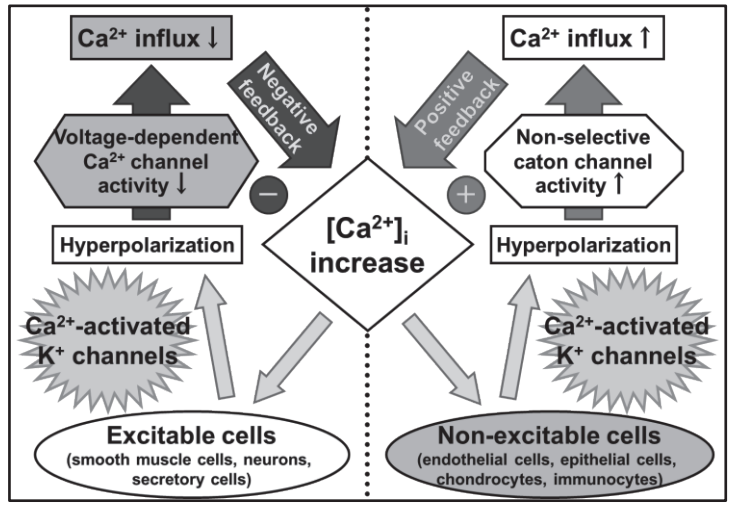

Fig.2 Positive and negative feedback mechanisms for $[Ca^{2+}]_i$ regulation

In contrast to the negative feedback mechanisms for $[Ca^{2+}]_i$ regulation in excitable cells, the regulation in non-excitable cells is positively feedbacked via the potentiation of Ca^{2+} activated K^+ channels and subsequently nonselective cation channels (Fig. 2). We demonstrated that such negative feedback mechanism for $[Ca^{2+}]_i$ regulation is rather ubiquitously functional in several types of non-excitable cells. This mechanism often contributes substantially to cell proliferation, differentiation or occasionally cell death in these cells.

We also clarified the relations between changes in ion channel activities and pathophysiology in many types of disease model animals to find out targets of drug discovery for the therapeutics. In addition, a new high throughput screening system for discovery of drugs acting on ion channels has been developed (patented in five countries) and is provided for ongoing screening.

I would like to express my sincere gratitude to so many collaborators in the researches presented here.